PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Early Detection and Progression of Subclinical Atherosclerosis in Psoriasis (EDSAP): Protocol for an observational, single-center, prospective cohort study.
AUTHORS	González-Cantero, Álvaro; Abbad- Jaime de Aragón, Carlota; Berna-Rico, Emilio; Ballester-Martinez, María Asunción; Jaén, Pedro; Solís, Jorge; G. Barderas, María; Fernández- Friera, Leticia; N Mehta, Nehal; Gelfand, Joel

VERSION 1 – REVIEW

REVIEWER	Hjuler, Kasper Aarhus Universitetshospital, Department of Dermatology, National Center for Autoimmune Diseases
REVIEW RETURNED	18-Apr-2023

GENERAL COMMENTS	This is a relevant study that builds on the concept of increased CV risk in psoriasis. I look forward to seeing the results as they emerge. I suggest adding a schedule of trial procedures overview to the methods section. While the author has made extensive references to their own work, it would be beneficial to also incorporate more citations from other relevant authors. The current reference list appears to be somewhat one-sided and could benefit from a more diverse range of sources. E.g. sections regarding previous CCTA results in psoriasis and the impact of biologics.

REVIEWER	Neema, Shekhar Armed Forces Medical College
REVIEW RETURNED	18-Jun-2023

GENERAL COMMENTS	Dear Authors, A well-designed study. However, the following needs to be addressed. 1. Authors have not discussed improvement in PASI 2. How do you analyse this data in case of primary or secondary failure? 3. CVD risk factors such as diabetes and hypertension are exclusion criteria. What happens to patients who are detected as diabetic or hypertensive during baseline evaluation. Do you exclude those too? This actually excludes patients most at risk and will benefit most from the intervention. 4. Are there any known -omics markers for atherosclerosis?

VERSION 1 – AUTHOR RESPONSE

Reviewers' comments:
Reviewer: 1

Dr. Kasper Hjuler, Aarhus Universitetshospital Comments to the Author: This is a relevant study that builds on the concept of increased CV risk in psoriasis. I look forward to seeing the results as they emerge.

I suggest adding a schedule of trial procedures overview to the methods section.

While the author has made extensive references to their own work, it would be beneficial to also incorporate more citations from other relevant authors. The current reference list appears to be somewhat one-sided and could benefit from a more diverse range of sources. E.g. sections regarding previous CCTA results in psoriasis and the impact of biologics.

Response: We thank the reviewer for taking the time to go through the manuscript and for the interest shown in our work.

We agree with you on increasing the variability of the reference sources, to increase the reliability of the paper. For this reason, we have added new references that expand the information in this regard.

Line 97: https://pubmed.ncbi.nlm.nih.gov/26093174/
Line 97: https://pubmed.ncbi.nlm.nih.gov/33978283/
Line 132: https://pubmed.ncbi.nlm.nih.gov/27385305/

We would also like to thank you for the detailed mention of the schedule of the study. In the present version, you will find the graphic summary of the study procedures in the methods section, as suggested. These figures are uploaded in different files from the manuscript.

Line 156 (Figure 1): EDSAP study flow. CCTA, coronary computed tomography angiography. 2D, 2-dimensional. 3D, 3-dimensional.
Line 181 (Figure 2): Participant timeline. This flow diagram illustrates the participant timeline including enrollment, baseline and 1-year follow up visits, the analysis of data and publication of results.

Reviewer: 2

Dr. Shekhar Neema, Armed Forces Medical College Comments to the Author: Dear Authors, A well-designed study. However, the following needs to be addressed.

1. Authors have not discussed improvement in PASI
2. How do you analyse this data in case of primary or secondary failure?

Response: We are very grateful for this interesting comment. As this is an observational cohort study, PASI will be monitored over time at each study visit and will be taken into account in all analyses. Other factors related to psoriasis will also be taken into consideration. Following your recommendation, we have made this clearer in the sections “Data collection”, “Clinical interview” and

"Physical examination, laboratory tests and biobanks". The relationship between improvement in PASI and coronary plaque modulation will also be explored, as it is now stated in “Discussion”. In addition, in the event that a change in biological treatment is necessary due to clinical practice, an exceptional visit will be scheduled for this purpose.

3. CVD risk factors such as diabetes and hypertension are exclusion criteria. What happens to patients who are detected as diabetic or hypertensive during baseline evaluation. Do you exclude those too? This actually excludes patients most at risk and will benefit most from the intervention.

Response: We are very grateful for this observation. We excluded patients who had hypertension or diabetes at baseline, because our aim is to study the specific impact of psoriasis itself on the development and progression of subclinical atherosclerosis, independent of other potential confounders such as diabetes, hypertension or other CVD risk factors.

4. Are there any known -omics markers for atherosclerosis?

Response: This approach is very interesting, thank you for highlighting this point. Currently, there are no specific proteomic markers validated for patients with psoriasis in clinical practice, justifying this study. For this purpose, the study comprises an unbiased discovery phase, involving matched patients, aimed at the discovery of previously unknown biomarkers and subsequent validation of these markers.

VERSION 2 – REVIEW

REVIEWER	Hjuler, Kasper Aarhus Universitetshospital, Department of Dermatology, National Center for Autoimmune Diseases
REVIEW RETURNED	25-Jul-2023

GENERAL COMMENTS	The mechanisms underlying the interplay between psoriasis and cardiovascular disease are complex. Although ambitious, this study may not fully elucidate this relationship. However, it will contribute another brick to the puzzle, advancing our understanding.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2 queried "How do you analyse this data in case of primary or secondary failure?" Please ensure this point is addressed.

Response: Thank you very much for this observation. We are sorry we did not make this clear in the previous reply. In case of primary or secondary failure, an exceptional visit will be scheduled in order to change treatment. As this is an observational study, this event would be part of routine clinical practice and the change of treatment will be made according to the criteria of the attending physician, based on the patient's previous history and the clinical characteristics of the patient.

These further clarifications can be found in line 174 of the present manuscript, in the “Data Collection” section.

Reviewer(s)' Comments to the Author:

Reviewer: 1
Dr. Kasper Hjuler, Aarhus Universitetshospital
Comments to the Author:The mechanisms underlying the interplay between psoriasis and cardiovascular disease are complex. Although ambitious, this study may not fully elucidate this relationship. However, it will contribute another brick to the puzzle, advancing our understanding.

Response: We thank you for your thoughtful observation. We fully agree that the mechanisms underlying the interaction between psoriasis and cardiovascular disease are complex. This study is ambitious in its scope, and may not fully elucidate this relationship. However, we believe this study is innovative in its approach. It uses a comprehensive dataset to assess cardiovascular disease in patients with psoriasis, as well as the role of inflammation.

We modestly believe that this study could be an important step in understanding the interaction between psoriasis and cardiovascular disease, and that our findings could provide a new roadmap for future research in this field.

Reviewer: 1
Competing interests of Reviewer: None